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Case Report

X-linked hypophosphatemia in the presence of a *CLDN16* variant: implications for renal handling and disease severity

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Abstract

X-linked hypophosphatemia (XLH), a rare genetic disorder caused by *PHEX* mutations, leads to fibroblast growth factor 23–mediated phosphate wasting, hypophosphatemia, and impaired bone mineralization. We report a 28-year-old woman with XLH carrying a heterozygous *PHEX* c.1080-1G>A splice-site mutation and a *CLDN16 c.165_166delinsC* mutation. Diagnosed at 18 months of age, she received long-term phosphate and active vitamin D metabolites, which resulted in secondary hyperparathyroidism, vertebral fractures, and medullary nephrocalcinosis requiring subtotal parathyroidectomy. Although *CLDN16* mutation carriers are usually asymptomatic, coexistence of XLH and prolonged phosphate therapy may exacerbate renal magnesium and calcium handling defects, potentially contributing to nephrocalcinosis. Burosumab was initiated for ongoing complications. Before surgery, she was wheelchair dependent due to severe diffuse bone pain. Postoperatively, pain improved and she regained independent ambulation, which further improved after burosumab initiation. Laboratory findings showed partial but sustained improvements in serum phosphate, alkaline phosphatase, and parathyroid hormone levels. Incomplete biochemical normalization may reflect renal tubular acidosis and medullary calcinosis. This case suggests long-term phosphate therapy can adversely affect parathyroid glands and may exacerbate nephrocalcinosis in the presence of tubular vulnerabilities. It supports burosumab as an effective therapeutic option in patients with coexisting renal tubular disorders.

Key Words X-linked hypophosphatemia, *PHEX*, *CLDN16*, burosumab, hyperparathyroidism

Abbreviations: 1,25[OH]$_2$D, 1,25-dihydroxyvitamin D; ALP, alkaline phosphatase; ATA, renal tubular acidosis; FGF23, fibroblast growth factor 23; GFR, glomerular filtration rate; PTH, parathyroid hormone; tCO_2, total carbon dioxide; XLH, X-linked hypophosphatemia.

Introduction

X-linked hypophosphatemia (XLH) is the most common hereditary form of rickets, caused by pathogenic variants in the phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene. These mutations increase fibroblast growth factor 23 (FGF23) activity, resulting in chronic renal phosphate wasting and impaired vitamin D activation. Affected individuals develop hypophosphatemia and impaired bone mineralization with skeletal deformities [1]. Standard treatment with oral phosphate and active vitamin D metabolites improves growth and bone health but can cause nephrocalcinosis and secondary hyperparathyroidism [2].

Burosumab, a human monoclonal antibody–inhibiting FGF23, has emerged as a targeted therapy for XLH. Recent international guidelines recommend burosumab over conventional therapy with phosphate and active vitamin D metabolites in adults with XLH presenting with fractures or pseudofractures [3]. Its efficacy in restoring phosphate homeostasis and improving skeletal and functional outcomes has been demonstrated in clinical trials [4, 5]. However, clinical experience in patients with coexisting renal tubular dysfunction or additional genetic variants remains limited.

The claudin-16 (*CLDN16*) gene encodes a tight junction protein in the thick ascending limb of the loop of Henle, essential for renal magnesium and calcium reabsorption [6]. Pathogenic variants cause familial hypomagnesemia with hypercalciuria and nephrocalcinosis (OMIM #603959) [7]. Although heterozygous carriers are typically asymptomatic, the coexistence of PHEX mutations may result in a more complex phenotype with combined

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phosphate, calcium, and magnesium disturbances. We describe a case of XLH with a heterozygous *CLDN16* mutation, complicated by nephrocalcinosis and hyperparathyroidism, showing improvement after burosumab.

Case presentation

A 28-year-old woman with XLH presented with progressive musculoskeletal pain and impaired mobility. Diagnosed at 18 months of age, she received long-term phosphate and calcitriol, which failed to prevent phosphate losses during critical growth periods, particularly puberty, leading to skeletal deformities. There was no history of consanguineous marriage or parathyroid disease in her family. Despite multiple corrective osteotomies and fixation for femoral and pelvic fractures, deformities recurred with residual abnormalities. Her condition deteriorated: height decreased from 137 to 129 cm, kyphosis worsened, and hip arthritis caused severe pain, limiting walking short distances. Progressive weakness and mobility loss rendered her wheelchair dependent.

Genetic testing, performed at Seoul National University Hospital, using a next-generation sequencing–based gene panel, confirmed a pathogenic heterozygous splice-site mutation in *PHEX* (c.1080-1G>A), consistent with X-linked dominant XLH. Additionally, a heterozygous frameshift mutation in *CLDN16* (c.165_166delinsC, p.Arg55Serfs*) was identified and classified as likely pathogenic.

Diagnostic assessment

Laboratory evaluations revealed: serum phosphate 2.3 mg/dL (Système International d'Unités [SI]: 0.74 mmol/L) (reference range, 2.5-4.5 mg/dL [SI: 0.81-1.45 mmol/L]), calcium 9.1 mg/dL (SI: 2.27 mmol/L) (reference range, 8.5-10.5 mg/dL [SI: 2.12-2.62 mmol/L]), alkaline phosphatase (ALP) 1975 IU/L (SI: 32.92 μkat/L) (reference range, 52-133 IU/L [SI: 0.87-2.22 μkat/L]), parathyroid hormone (PTH) 1848 pg/mL (SI: 194.59 pmol/L) (reference range, 17.3-74.1 pg/mL [SI: 1.8-7.8 pmol/L]), serum magnesium 1.68 mg/dL (SI: 0.69 mmol/L) (reference range, 1.82-2.92 mg/dL [SI: 0.75-1.20 mmol/L]), ionized magnesium 1.05 mg/dL (SI: 0.43 mmol/L) (reference range, 1.09-1.46 mg/dL [SI: 0.45-0.60 mmol/L]), and 25-hydroxyvitamin D 12.34 ng/mL (SI: 30.85 nmol/L) (reference range, 30-60 ng/mL [SI: 75-150 nmol/L]). Analysis of fasting serum and spot urine samples showed that the tubular reabsorption of phosphate was 0.538, yielding a corrected TmP/glomerular filtration rate (GFR) of 1.24 mg/dL (SI: 0.40 mmol/L) (reference range, 2.8-4.2 mg/dL [SI: 0.90-1.35 mmol/L]). Serum creatinine was 0.66 mg/dL (SI: 58 μmol/L) (reference range, 0.49-0.91 mg/dL [SI: 43-80 μmol/L]), with an estimated GFR (eGFR) of 123 mL/min/1.73 m^2. The spot urine calcium was 9.1 mg/dL. Twenty-four-hour urine studies showed levels of calcium 100 mg/day and magnesium 2.45 mmol/day that were inconsistent with clinically significant hypercalciuria or hypermagnesuria.

Spinal imaging revealed symmetrical biconcave deformities of multiple vertebral bodies (codfish vertebrae) with accentuated thoracic kyphosis and diffuse osteopenia (Fig. 1A and 1B). Pelvic radiographs showed internal fixation of a left femoral neck fracture with bilateral coxa vara and periarticular osteopenia (Fig. 1C). Dual-energy X-ray absorptiometry revealed *Z*-scores of −1.3 at the lumbar spine (artifactually elevated due to deformities), −3.2 at the femoral neck, and −3.8 at the total hip. Renal imaging revealed bilateral medullary nephrocalcinosis with stones (Fig. 2). Distal renal tubular acidosis (RTA) was suggested by normal anion gap metabolic acidosis, with serum total carbon dioxide (tCO_2) of 19 mmol/L (reference range, 24-30 mmol/L), a positive urine anion gap, and urine pH 6.5. Twenty-four-hour urine analysis showed nonalbuminuric proteinuria without glucosuria or marked phosphaturia and low-citrate excretion. Hypokalemia (3.3 mmol/L) and low tCO_2 improved with bicarbonate and potassium citrate therapy.

The clinical course was complicated by severe secondary hyperparathyroidism (peak PTH 2383 pg/mL [SI: 250.9 pmol/L]), persistent hypophosphatemia, nephrocalcinosis, new-onset hypertension, and multiple vertebral fractures. Neck ultrasound and parathyroid single-photon emission computed tomography–computed tomography (CT) revealed bilateral upper pole nodules (Fig. 3). Subtotal parathyroidectomy was performed in April 2024 for refractory secondary hyperparathyroidism. Prior to surgery, the patient was treated with cinacalcet 25 mg orally (December 2023 to April 2024); however, PTH levels remained markedly elevated. The left upper, left lower, and right upper parathyroid glands were excised, and histopathological examination revealed nodular parathyroid hyperplasia. Immediately before surgery, phosphate was 1.7 mg/dL (SI: 0.55 mmol/L), PTH 1152 pg/mL (SI: 121.31 pmol/L), and ALP 695 IU/L (SI: 11.58 μkat/L). Postoperatively, phosphate transiently increased to 3.0 mg/dL (SI: 0.97 mmol/L), PTH decreased to 135 pg/mL (SI: 14.22 pmol/L), and ALP dropped to 581 IU/L (SI: 9.68 μkat/L), but these values relapsed within weeks, and phosphate declined below 2.0 mg/dL (1.7 mg/dL [SI: 0.55 mmol/L]), accompanied by elevated PTH (286 pg/mL [SI: 30.12 pmol/L]) and ALP (426 IU/L [SI: 7.11 μkat/L]) (Fig. 4). Despite partial biochemical improvement, serum phosphate remained subnormal during follow-up, and the patient continued to experience bone pain and gait impairment. Conventional therapy with phosphate and calcitriol was continued until burosumab was administered in July 2024.

Treatment

Burosumab therapy was initiated at ∼1 mg/kg every 4 weeks, and a 30 mg dose was administered based on a body weight of 35.0 kg (height 127.0 cm). Although burosumab has been approved for XLH in South Korea since September 2020, reimbursement has been limited to pediatric patients; therefore, its use in adult patients remains challenging in routine clinical practice.

Outcome and follow-up

Parathyroid hormone levels fluctuated following subtotal parathyroidectomy but showed a more stable and favorable trend after burosumab initiation. With limited phosphate response, persistent symptoms, and modest weight gain, burosumab dose was increased from 30 to 40 mg in November 2024, and treatment continued through September 2025. Serial monitoring demonstrated partial but sustained biochemical improvement: serum phosphate increased from 1.7 mg/dL (SI: 0.55 mmol/L)

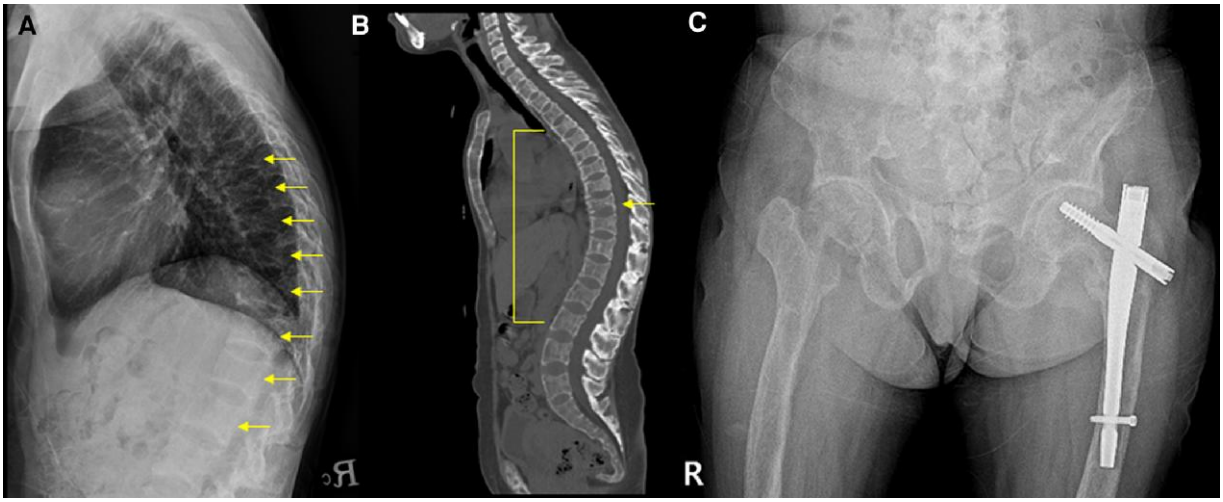

Figure 1 Radiologic findings of the spine and pelvis. (A) Lateral thoracic spine radiograph showing symmetrical biconcave deformities of multiple vertebral bodies (codfish vertebrae), consistent with osteomalacia. (B) Sagittal CT image demonstrating diffuse biconcave vertebral deformities with accentuation of kyphosis. Arrows indicate representative biconcave deformities of the vertebral bodies, and yellow lines delineate the extent of vertebral levels affected by these deformities. (C) Pelvic anteroposterior radiograph showing internal fixation of a left femoral neck fracture, with bilateral coxa vara and periarticular osteopenia.

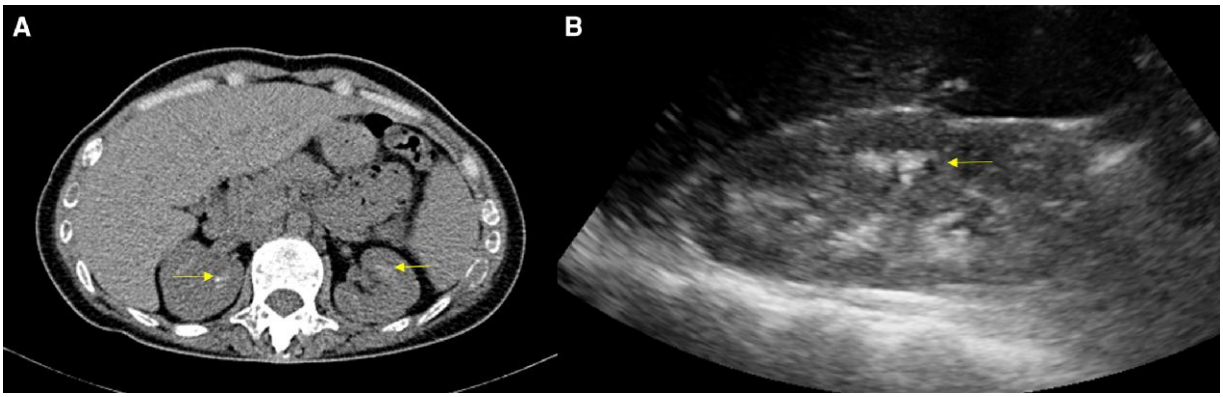

Figure 2 Genitourinary CT and renal ultrasonography findings. (A) Axial CT image demonstrating bilateral medullary nephrocalcinosis with renal calyceal stones (arrows). (B) Renal ultrasonography showing increased echogenicity in both kidneys, consistent with medullary nephrocalcinosis (arrow).

to 2.1 mg/dL (SI: 0.68 mmol/L), ALP decreased from 426 IU/L (SI: 7.12 μkat/L) to 281 IU/L (SI: 4.69 μkat/L), and PTH declined from 286 pg/mL (SI: 30.12 pmol/L) to 157 pg/mL (SI: 16.52 pmol/L). Serum magnesium levels remained at or slightly below the lower limit of the normal range during follow-up, requiring intermittent oral magnesium supplementation (Table 1). Baseline 1,25-dihydroxyvitamin D (1,25$[OH]_2$D) levels were not available. The 1,25$(OH)_2$D level measured in March 2025 was 44.9 pg/mL (SI: 116.6 pmol/L) (reference range, 19.9-79.3 pg/mL [SI: 48-206 pmol/L]) without calcitriol replacement. Serum creatinine decreased from 1.06 mg/dL (SI: 94 μmol/L) to 0.86 mg/dL (SI: 76 μmol/L), with a corresponding increase in eGFR from 73 to 94 mL/min/1.73 m^2. By September 2025, serum phosphate was 3.0 mg/dL (SI: 0.97 mmol/L), calcium 8.6 mg/dL (SI: 2.15 mmol/L), and ALP 233 IU/L (SI: 3.89 μkat/L).

The patient reported a substantial symptomatic improvement. Three months after the subtotal parathyroidectomy, her pain decreased from 10/10 to (2 to 3)/10 on the visual analog scale, although ambulatory limitations persisted and she continued to require a walker. After the initiation of burosumab therapy, gait stability improved and she subsequently achieved slow independent ambulation with further reduction in bone pain. Approximately 1 year after starting burosumab (July 2025), she demonstrated meaningful gains in functional strength, including improved handgrip strength facilitating daily activities. No serious adverse effects were observed.

Discussion

We present a case of XLH due to a pathogenic *PHEX* mutation, coexisting with a heterozygous *CLDN16* frameshift variant, characterized by complex skeletal, biochemical, and renal complications following long-term conventional therapy. The patient developed severe secondary hyperparathyroidism refractory to phosphate, active vitamin D metabolites, and cinacalcet, and was transitioned to burosumab after subtotal

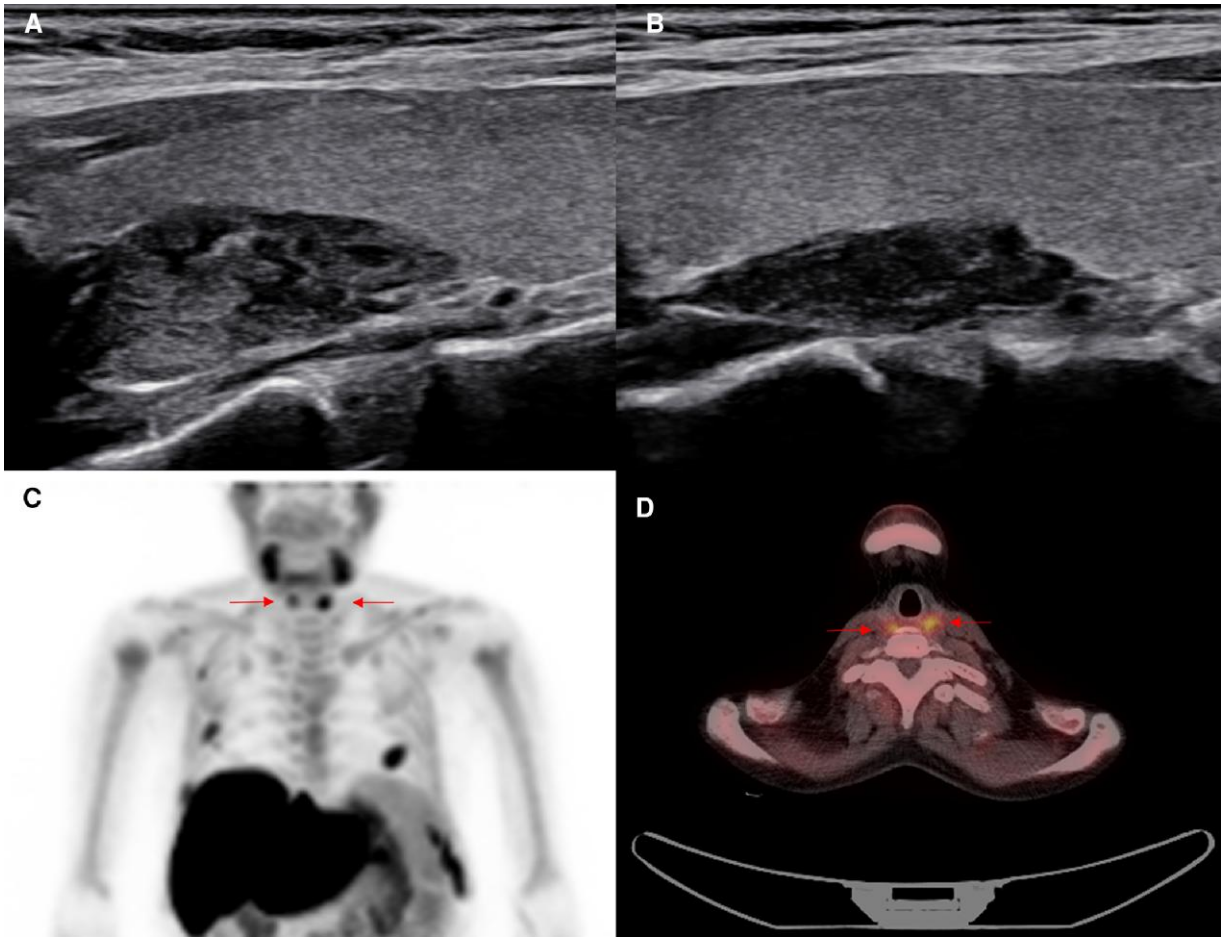

Figure 3 Imaging of parathyroid nodules. (A, B) Neck ultrasonography showing hypoechoic nodules at the upper poles of the left and right thyroid lobes. (C) ^{18}F-fluorocholine positron emission tomography (PET)/CT (maximum intensity projection) demonstrating increased radiotracer uptake in extrathyroidal nodules at both upper poles (arrows). (D) Axial fused PET/CT image confirming focal radiotracer uptake in an extrathyroidal nodule (arrows).

parathyroidectomy for persistent hypophosphatemia and functional impairment.

Conventional therapy with phosphate and active vitamin D metabolites improves outcomes but often fails to control disease and induces nephrocalcinosis or hyperparathyroidism, especially with early initiation or high-dose use [8-11]. Burosumab was introduced to address persistent hypophosphatemia and functional impairment after parathyroid surgery. It restores phosphate homeostasis without the nephrotoxic and endocrine adverse effects associated with traditional treatment [4]. After 6 months of therapy, the patient showed gradual but incomplete improvement in serum phosphate, ALP, and PTH levels.

Clinical manifestation of CLDN16-related disease is typically the result of biallelic mutations; however, substantial phenotypic variability has been reported even among patients carrying identical pathogenic variants [6]. In the present case, the heterozygous CLDN16 frameshift variant could be interpreted as a potential genetic modifier, adding complexity to the renal phenotype rather than acting as a primary pathogenic factor. Experimental studies have shown that CLDN16 mutations impair paracellular magnesium transport in the thick ascending limb [7]. Coexisting distal RTA may also contribute to the attenuated biochemical response to burosumab. Although a direct association between heterozygous CLDN16 variants and distal RTA has not been established, incomplete distal RTA has been reported in patients with CLDN16-related familial hypomagnesemia with hypercalciuria and nephrocalcinosis [12]. Recent studies have reported that genetic variants affecting proximal tubular phosphate handling may influence the clinical severity of XLH, including greater functional impairments associated with polymorphisms in phosphate transport–related genes [13].

According to international guidelines for adult XLH, burosumab aims to improve renal phosphate handling, maintain serum phosphate within the low-to-mid normal range while avoiding hyperphosphatemia, normalize ALP, promote fracture healing, and relieve musculoskeletal symptoms [3, 14, 15]. These guidelines emphasize that clinical improvement can occur even without complete biochemical normalization. In our patient, despite persistently subnormal phosphate levels, marked reduction in pain, restoration of mobility, and gradual biochemical improvement were observed, consistent with these recommendations.

Emerging evidence suggests that burosumab is renally safe and may offer additional metabolic or cardiovascular benefits, although long-term data in complex adult cases remain limited [16-18]. In line with current guidelines, burosumab may be

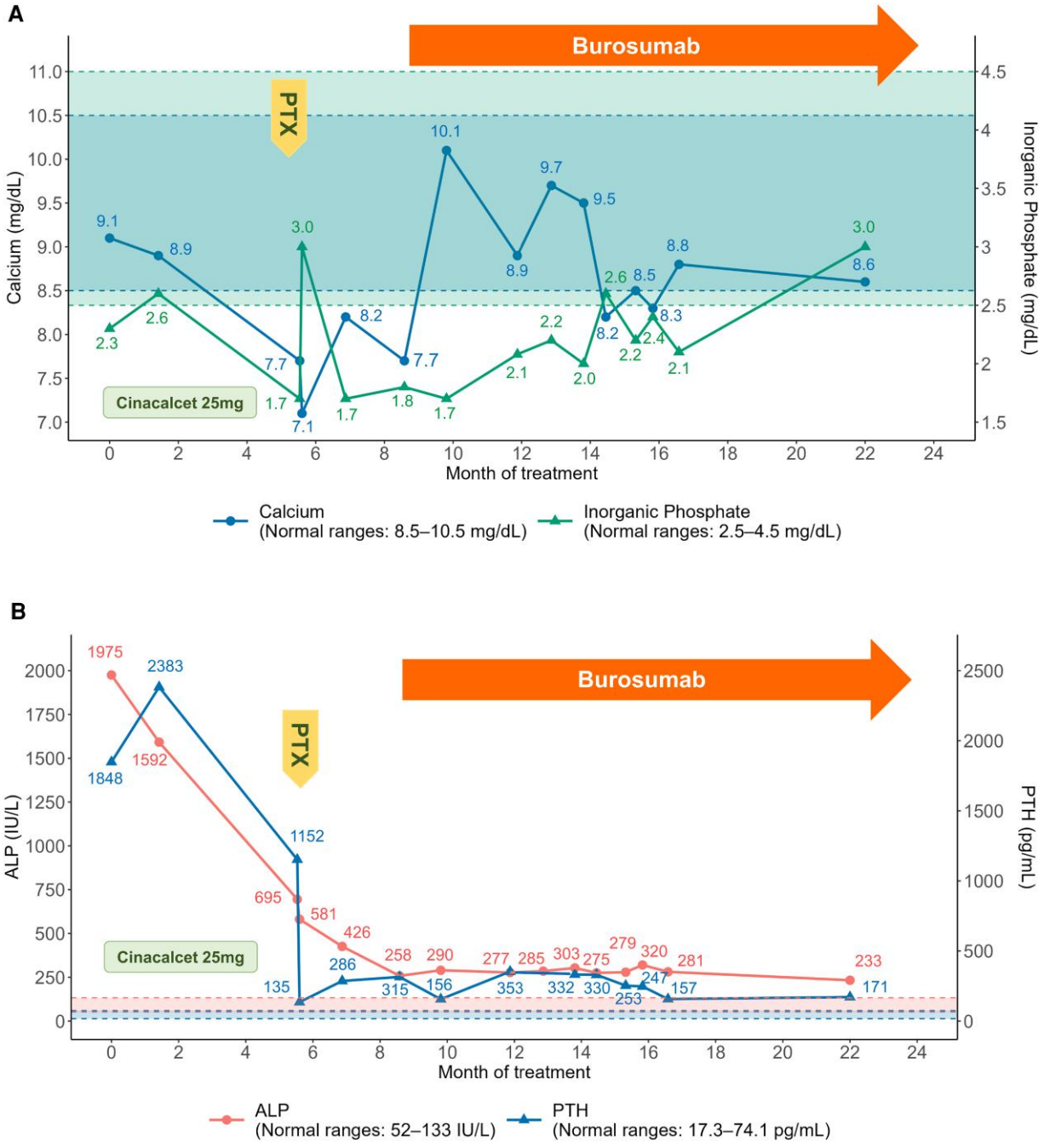

Figure 4 Serial biochemical changes before and after subtotal parathyroidectomy (PTX) and burosumab treatment. (A) Serum calcium and phosphate levels (mg/dL). (B) ALP (IU/L) and PTH (pg/mL). The downward arrow indicates the timing of subtotal PTX, and the horizontal arrow represents the period of burosumab therapy.

Table 1 Chronological changes in serum magnesium levels in relation to treatment

Date	Clinical course	Serum magnesium (mg/dL [mmol/L])	Reference range (mg/dL [mmol/L])
March 2024	Before parathyroidectomy	1.68 [0.69]	1.82-2.92 [0.75-1.20]
July 2024	After parathyroidectomy, before burosumab	1.63 [0.67]	1.82-2.92 [0.75-1.20]
January 2025	After burosumab initiation (30 mg every 4 weeks)	1.92 [0.79]	1.82-2.92 [0.75-1.20]
June 2025	After burosumab dose escalation (40 mg every 4 weeks)	1.65 [0.68]	1.82-2.92 [0.75-1.20]

considered in patients with renal complications, with regular renal monitoring recommended.

This case highlights the clinical complexity of XLH, particularly in the presence of additional renal tubular variants. Although a causal relationship could not be established, the coexistence of a heterozygous *CLDN16* variant may have added complexity to the renal phenotype of this patient. Clinicians should consider the potential genetic modifiers in patients with atypical features or suboptimal treatment responses, and next-generation sequencing–based gene panels targeting renal tubular transport genes may be considered in selected cases. Further studies are needed to clarify the long-term efficacy and safety of burosumab in patients with renal or metabolic comorbidities.

Learning points

- Long-term phosphate therapy in XLH can lead to hyperparathyroidism and requires careful monitoring.
- Burosumab is an effective treatment for adults with XLH, especially when conventional therapy is insufficient or poorly tolerated.
- Additional genetic variants may complicate the clinical course of XLH; individualized management and timely transition to burosumab help prevent complications and improve quality of life.

Contributors

All authors made individual contributions to authorship. S.A.J. and Y.R. were involved in the diagnosis and management of the patient and acquisition of clinical and laboratory data. S.A.J. drafted the manuscript. K.M.K. contributed to the conception of the case report, interpretation of the clinical findings, and critical revision of the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Informed patient consent for publication

Signed informed consent was obtained directly from the patient for publication.

Data availability

Original data generated and analyzed for this case report are included in this published article.

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